Adaptive randomised controlled non-inferiority multicentre trial (the Ketodex Trial) on intranasal dexmedetomidine plus ketamine for procedural sedation in children: study protocol

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ABSTRACT

Introduction Up to 40% of orthopaedic injuries in children require a closed reduction, almost always necessitating procedural sedation. Intravenous ketamine is the most commonly used sedative agent. However, intravenous insertion is painful and can be technically difficult in children. We hypothesise that a combination of intranasal dexmedetomidine plus intranasal ketamine (Ketodex) will be non-inferior to intravenous ketamine for effective sedation in children undergoing a closed reduction.

Methods and analysis This is a six-centre, four-arm, adaptive, randomised, blinded, controlled, non-inferiority trial. We will include children 4–17 years with a simple upper limb fracture or dislocation that requires sedation for a closed reduction. Participants will be randomised to receive either intranasal Ketodex (one of three dexmedetomidine and ketamine combinations) or intravenous ketamine. The primary outcome is adequate sedation as measured using the Paediatric Sedation State Scale. Secondary outcomes include length of stay, time to wakening and adverse effects. The results of both per protocol and intention-to-treat analyses will be reported for the primary outcome. All inferential analyses will be undertaken using a response-adaptive Bayesian design. Logistic regression will be used to model the dose–response relationship for the combinations of intranasal Ketodex. Using the Average Length Criterion for Bayesian sample size estimation, a survey-informed non-inferiority margin of 17.8% and priors from historical data, a sample size of 410 participants will be required. Simulations estimate a type II error rate of 0.08 and a type I error rate of 0.047.

Ethics and dissemination Ethics approval was obtained from Clinical Trials Ontario for London Health Sciences Centre and McMaster Research Ethics Board. Other sites have yet to receive approval from their institutions. Informed consent will be obtained from guardians of all participants in addition to assent from participants. Study data will be submitted for publication regardless of results.

Strengths and limitations of this study

- This study employs a response adaptive trial design to overcome gaps in our current understanding of the most effective dosing combination of intranasal Ketodex.
- To optimise trial efficiency, frequent assessment of the data will be used to adapt the trial to increase the number of participants receiving the more effective combination of Ketodex.
- This study involved a patient engagement strategy whereby patient partners informed the eligibility criteria and outcomes, and reviewed letters of information, consent and assent.
- We expect that current translation to practice may be limited by the high volume of intranasal drug required for older children unless a higher concentration of ketamine (100 mg/kg) becomes widely available.
- Research nurses may become aware of group assignment and blinding will only be possible for outcome assessors.

Trial registration number NCT0419525.

INTRODUCTION

Orthopaedic injuries comprise more than 10% of emergency department (ED) visits in children,1,2 and 25%–50% of children will sustain a fracture before the age of 16 years.3 Between 20% and 40% of extremity fractures in children require a closed reduction,4,5 often necessitating procedural sedation. The demand for procedural sedation in children outside the operating room is increasing at a rate of 10% annually.6,7 As such, the
placement of an intravenous catheter for procedural sedation is extremely common. However, children rate intravenous insertion as one of the most painful hospital experiences, second only to the painful condition itself. Intravenous insertion can be more technically difficult in children because of smaller veins and lack of cooperation, often leading to multiple intravenous attempts.

Intranasal medications may obviate the need for distressing intravenous placement and offer a technically easier and pain-free approach to procedural sedation. This may have widespread applicability in patients with difficult intravenous access, resource-limited settings, needle phobia or when experience placing an intravenous is limited. Ketamine is the most commonly used sedative agent for fracture reduction in children and intranasal ketamine has been found to be effective for fracture pain, some procedural pain, anaesthetic preinduction and diagnostic imaging. However, neither agent has been studied for procedural sedation to reduce fractures or dislocations. Dexmedetomidine is a central alpha 2-adrenergic receptor agonist with analgesic and anxiolytic properties and is effective for procedural anxiety in children in its intravenous form. A recent systematic review of intranasal dexmedetomidine in children undergoing painful procedures (dental procedures, venipuncture and laceration repair) found doses ranging from 1 to 4 mcg/kg were well tolerated and superior to conventional sedatives (oral chloral hydrate and oral and intranasal midazolam) in providing adequate sedation.

However, procedural sedation for orthopaedic reductions may require agents with greater sedative and analgesic potency. Preliminary evidence suggests that a combination of dexmedetomidine and ketamine may be superior than either agent alone. A combination of intranasal ketamine and intranasal dexmedetomidine (‘Ketodex’) theoretically combines the analgesic efficacy of ketamine with the sedative efficacy of dexmedetomidine. However, there remains uncertainty regarding the ideal combination of these two agents. In order to provide robust evidence supporting an alternate approach that precludes the need for an intravenous in children undergoing sedation, a response-adaptive Bayesian design will be used to determine the most effective combination of Ketodex and to test our hypothesis of whether this combination is non-inferior to intravenous ketamine.

**METHODS AND ANALYSIS**

**Design**

This is a six-centre, four-arm, randomised, blinded, double-dummy, controlled, parallel group, adaptive dose-finding, non-inferiority, phase II/III trial. The trial will determine whether intranasal Ketodex is non-inferior to intravenous ketamine for children undergoing procedural sedation and analgesia determine the optimal dosing combination for intranasal Ketodex. The study protocol is reported using the SPIRIT-PRO reporting guidelines.

**Study setting**

This study will be conducted in six paediatric EDs across Canada: (1) Children’s Hospital at London Health Sciences Centre (London, Ontario) (coordinating site); (2) Stollery Children’s Hospital (Edmonton, Alberta); (3) BC Children’s Hospital (Vancouver, British Columbia); (4) Winnipeg Children’s Hospital (Winnipeg, Manitoba); (5) CHEO (Ottawa, Ontario); and (6) McMaster Children’s Hospital (Hamilton, Ontario). The annual ED census for recruiting centres ranges from 30000 to 70000 patient visits.

**Eligibility**

Children will be eligible if they meet all of the following criteria: (1) provision of signed and dated informed consent form; (2) stated willingness to comply with all study procedures and availability for the duration of the study; (3) deemed by treating physician to require procedural sedation; (4) aged 4–17 years; (5) weighing up to 60 kg; (6) one of the following injuries: forearm fracture, metacarpal or phalangeal fracture, or dislocation of a shoulder or elbow; (7) closed reduction expected to take no more than 5 minutes to reduce (as determined by the procedure physician and not including cast or splint application); and (8) both nares are fully patent. Exclusion criteria are listed in table 1.

**Interventions and permissible co-interventions**

Eligible participants will be randomised to intranasal Ketodex or intravenous ketamine with a 3:2 allocation ratio. Participants receiving intranasal Ketodex will be further adaptively randomised to three alternative combinations where the randomisation ratio is proportional to the posterior probability that a combination is optimal in terms of providing adequate sedation. A double-dummy approach will be used to overcome the possibility of unmasking due to perceptible differences in interventional routes. This involves each participant receiving both an intranasal and intravenous intervention, only one of which is the real drug. Both intranasal and intravenous interventions will be administered through any of the following:

1. Dexmedetomidine (Pfizer, Kirkland, Quebec), single dose, 4 mcg/kg (0.04 mL/kg) of 100 mcg/mL solution, maximum of 200 mcg (2 mL), then ketamine (Sandoz, Mississauga, Ontario), single dose, 2 mg/kg (0.04 mL/kg) of 50 mcg/mL solution, maximum of 200 mg (4 mL) (D4K2), both delivered intranasally using a mucosal atomiser device (MAD) and divided to both nares and 0.9% normal saline 0.03 mL/kg delivered intravenously to a maximum of 2 mL.

2. Dexmedetomidine (Pfizer), single dose, 3 mcg/kg (0.03 mL/kg) of 100 mcg/mL solution, maximum of 200 mcg (2 mL), then ketamine (Sandoz), single dose, 3 mg/kg (0.06 mL/kg) of 50 mcg/mL solution, maximum of 300 mcg (6 mL) (D3K3), both delivered intranasally using MAD and divided to both nares and 0.9%
**Table 1**  Trial registration dataset

<table>
<thead>
<tr>
<th>Data category</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary registry and trial identifying number</td>
<td>clinicaltrials.gov</td>
</tr>
<tr>
<td>Date of registration in primary registry</td>
<td>15 August 2019</td>
</tr>
<tr>
<td>Secondary identifying numbers</td>
<td>Clinical Trials Ontario # 1987</td>
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</tbody>
</table>
| Sources of monetary or material support           | Canadian Institutes of Health Research SPOR Innovative Clinical Trials Grant (MYG-151207)  
Academic Medical Organisation of Southwestern Ontario 
Ontario Ministry of Economic Development, Job Creation and Trade Early Researcher Award |
| Primary sponsor                                   | Lawson Health Sciences Research Institute                                    |
| Secondary sponsor                                 | –                                                                            |
| Contact for public queries                        | Dr Naveen Poonai, naveen.poonai@lhsc.on.ca                                   |
| Contact for scientific queries                    | Dr Naveen Poonai, naveen.poonai@lhsc.on.ca                                   |
| Public title                                      | The Ketodex study                                                           |
| Scientific title                                  | Adaptive randomised controlled non-inferiority multicentre trial (the Ketodex trial) on intranasal dexmedetomidine plus ketamine for procedural sedation in children study protocol |
| Countries of recruitment                          | Canada                                                                       |
| Health conditions or problems studied             | Fracture, dislocation                                                       |
| Interventions                                     | 1. Dexmedetomidine (Pfizer, Kirkland, Quebec), single-dose, 4 mcg/kg (0.04 mL/kg) of 100 mcg/mL solution, maximum of 200 mcg (2 mL), then ketamine (Sandoz, Mississauga, Ontario), single dose, 2 mg/kg (0.04 mL/kg) of 50 mg/mL solution, maximum of 200 mg (4 mL) (D4K2), both delivered intranasally using a MAD and divided to both nares, and 0.9% normal saline 0.03 mL/kg delivered intravenously to a maximum of 2 mL or  
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3. Dexmedetomidine (Pfizer), single dose, 2 mcg/kg (0.02 mL/kg) of 100 mcg/mL solution, maximum of 200 mcg (2 mL) then ketamine (Sandoz), single dose, 4 mg/kg (0.08 mL/kg) of 50 mg/mL solution, maximum of 400 mg (8 mL) (D2K4), both delivered intranasally using MAD and divided to both nares and 0.9% normal saline 0.03 mL/kg delivered intravenously to a maximum of 2 mL or  
4. Ketamine, single dose, 1.5 mg/kg (0.03 mL/kg) of 50 mg/mL solution delivered intravenously, to a maximum of 100 mg (2 mL) and two aliquots of 0.9% normal saline in three possible combinations: (1) 0.04 mL/kg (max 2 mL) then 0.04 mL/kg (max 4 mL) (placebo D4K2), (2) 0.03 mL/kg (max 2 mL) then 0.06 mL/kg (max 6 mL) (placebo D3K3), (3) 0.02 mL/kg (max 2 mL) then 0.08 mL/kg (max 8 mL) (placebo D2K4), delivered intranasally using MAD and divided to both nares. |
Table 1  Continued

<table>
<thead>
<tr>
<th>Data category</th>
<th>Information</th>
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<tbody>
<tr>
<td>Key inclusion and exclusion criteria</td>
<td>General criteria</td>
</tr>
<tr>
<td>1.</td>
<td>Provision of signed and dated informed consent form.</td>
</tr>
<tr>
<td>2.</td>
<td>Stated willingness to comply with all study procedures and availability for the duration of the study.</td>
</tr>
<tr>
<td>3.</td>
<td>Deemed by treating physician to require procedural sedation.</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>1. Children presenting to the paediatric emergency departments of participating sites age 4–17 years.</td>
</tr>
<tr>
<td>2.</td>
<td>Weighing up to and including 60 kg.</td>
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<tr>
<td>3.</td>
<td>One of the following injuries:</td>
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<tr>
<td>4.</td>
<td>Forearm fracture.</td>
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<tr>
<td>5.</td>
<td>Metacarpal or phalangeal fracture.</td>
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<td>6.</td>
<td>Dislocation of a shoulder or elbow.</td>
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<td>7.</td>
<td>Closed reduction expected to take no more than 5 min of manipulation to reduce (as determined by the procedure physician and not including cast or splint application).</td>
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<td>8.</td>
<td>Both nares are fully patent.</td>
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<tr>
<td>Exclusion criteria</td>
<td>Previous hypersensitivity reaction to ketamine or dexmedetomidine including rash, difficulty breathing, hypotension, apnea or laryngospasm.</td>
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<td>9.</td>
<td>Suspected globe rupture.</td>
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<td>11.</td>
<td>Uncontrolled hypertension.</td>
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<td>12.</td>
<td>Nasal bone deformity or septal deviation.</td>
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<td>13.</td>
<td>Poor English or French fluency in the absence of native language interpreter.</td>
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<td>14.</td>
<td>American Society of Anesthesiologists Class III or greater.</td>
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<td>15.</td>
<td>Previous diagnosis of schizophrenia or active psychosis as per the treating physician.</td>
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<td>16.</td>
<td>Neurocognitive impairment that precludes the ability to self-report pain and satisfaction.</td>
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<tr>
<td>17.</td>
<td>More than one fracture or dislocation requiring reduction.</td>
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<tr>
<td>18.</td>
<td>Haemodynamic compromise as per the treating physician.</td>
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<tr>
<td>19.</td>
<td>Glasgow coma score &lt;15.</td>
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<tr>
<td>20.</td>
<td>Previous sedation with ketamine within 24 hours.</td>
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<tr>
<td>21.</td>
<td>Fracture is comminuted or associated with a dislocation.</td>
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<tr>
<td>22.</td>
<td>Participant has undergone a haematoma block within 24 hours.</td>
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<tr>
<td>23.</td>
<td>Previous enrolment in the trial.</td>
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<tr>
<td>25.</td>
<td>Congenital heart disease or known cardiac dysrhythmia.</td>
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<tr>
<td>26.</td>
<td>Known or suspected hepatic impairment.</td>
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<tr>
<td>27.</td>
<td>Known renal insufficiency.</td>
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<tr>
<td>28.</td>
<td>Uncorrected mineralocorticoid deficiency.</td>
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<tr>
<td>29.</td>
<td>Obstructive sleep apnoea.</td>
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</table>

Study type | Randomised, blinded, double-dummy, controlled, parallel group, adaptive dose-finding, non-inferiority, phase II/III trial |

Date of first enrolment | 11 March 2020 |
Sample size | 410 |
Recruitment status | Actively recruiting |
Data category | Information
--- | ---
Primary outcomes | Adequate sedation for the duration of the procedure. For closed reduction, this is defined as the interval of time from the first application of traction or manipulation of the injured limb for the purpose of anatomical realignment to the last application of a realigning force. Adequate is defined as fulfilment of all three of the following criteria:
1. A PSSS score of 2 or 3 for the duration of the procedure.
2. No additional medication is given during the procedure for the purpose of sedation.
3. The patient did not actively resist, cry or require physical restraint for completion of the closed reduction.

Key secondary outcomes | Length of stay (min): defined as the time recorded in the medical record between triage and discharge. This is an important consideration to the uptake of intranasal Ketodex in practice.
Time to wakening: defined as the duration of time between the first pair of intranasal sprays to the first PSSS score of >3, postclosed reduction.
AEs: AEs are based on Health Canada reporting standards. They include nasal irritation, which will be assessed using the Faces Pain Scale Revised immediately prior to discharge and maladaptive behaviours 24–48 hours postrecovery, which will be assessed using the PHBQ. The FPS-R will be administered using an iPad and the PHBQ will be administered through an automated email survey from REDCap or by telephone.

Other endpoints | 1. Length of stay due to PSA is the time interval between the first pair of intranasal sprays to discharge.
2. Duration of procedure is the time interval between the first pair of intranasal sprays/intravenous dose to the end of cast or splint application.
3. Length of stay is the time interval between triage assessment and discharge.
4. Caregiver, participant, bedside nurse or respiratory therapist, and physician satisfaction with sedation will be recorded at the index visit using a Visual Analogue Scale. For the caregiver and participant, the following questions will be posed immediately prior to discharge: how satisfied were you with your child’s sedation? (caregiver); how happy were you with your sleep? (participant). For the healthcare providers, the following question will be posed immediately following cast/splint application: how satisfied were you with the level of sedation in your patient?
5. Nasal irritation: discomfort associated with nasal sprays (if recalled), assessed by the research nurse using the FPS-R at discharge.
6. Volume of intranasal intervention received compared with volume of intranasal intervention calculated to be received will be recorded at the index visit.
7. Adjunctive intravenous therapy and medications (eg, analgesics, antibiotics, antiemetics and fluids) will be recorded at the index visit.
8. Presedation pain will be recorded by the research nurse from the participant using the FPS-R immediately prior to the first pair of intranasal sprays.
9. Patient preference for the method of sedation will be recorded at the index visit by asking the participant: if you were to be put to sleep again for an injury, what would you prefer, an intravenous needle or nasal sprays (choose one)?

Ethics review | Clinical Trials Ontario # 1987
Completion date | –
Summary results | –
IPD sharing statement | Deidentified data can be shared, on a case-by-case basis, on discussion with the principal investigator.
normal saline 0.03 mL/kg delivered intravenously to a maximum of 2 mL.

3. Dexmedetomidine (Pfizer), single dose, 2 mcg/kg (0.02 mL/kg) of 100 mcg/mL solution, maximum of 200 mcg (2 mL), then ketamine (Sandoz), single dose, 4 mg/kg (0.08 mL/kg) of 50 mg/mL solution, maximum of 400 mg (8 mL) (D2K4), both delivered intranasally using MAD and divided to both nares and 0.9% normal saline 0.03 mL/kg delivered intravenously to a maximum of 2 mL.

4. Ketamine, single dose, 1.5 mg/kg (0.03 mL/kg) of 50 mg/mL solution delivered intravenously, to a maximum of 100 mg (2 mL) and two aliquots of 0.9% normal saline in three possible combinations: (1) 0.04 mL/kg (max 2 mL) then 0.04 mL/kg (max 4 mL) (placebo D4K2), (2) 0.03 mL/kg (max 2 mL) then 0.06 mL/kg (max 6 mL) (placebo D3K3), and (3) 0.02 mL/kg (max 2 mL) then 0.08 mL/kg (max 8 mL) (placebo D2K4), delivered intranasally using MAD and divided to both nares.

Participants will be positioned in a recumbent supine position at 45°. Each pair of sprays will be separated by at least 60 s. The physician or their designate must administer the intravenous intervention 30–40 min after the intranasal dexmedetomidine/saline sprays. The research or bedside nurses will administer intranasal interventions, and the physician or their designate will administer intravenous interventions (figure 1).

All participants will receive continuous cardiorespiratory monitoring, consisting of five-lead continuous ECG, oxygen saturation and blood pressure, with consideration of capnography. This will commence immediately prior to administration of the intervention and will continue until the participant is awake.

The treating physician will not be permitted to prescribe any sedative, anxiolytic or analgesic co-intervention within 15 min of the study intervention. Analgesics for pain and antiemetics may be given at any time at the discretion of the clinician or nurse outside the procedural sedation period. Anxiolytics for emergence agitation or anxiety may be given following the closed reduction. Any prescribed home or over-the-counter medications may be given at any time during the index visit with the exception of sedatives.

Rescue sedation may be provided if, after 1 min following the intravenous intervention, either of the following conditions are met: (1) the participant is still responding to surroundings or (2) procedure has begun and the participant's vocalisations are consistent with pain, or the participant is withdrawing or localising to pain.

**Randomisation and allocation concealment**

Randomisation will be performed in two stages as follows:

1. First, the pharmacy at each site will randomise participants in a 3:2 allocation ratio to intranasal Ketodex or intravenous ketamine and will adapt a previously published design.23 This stage will be stratified by site and will be randomised in a block size known only to the statistical team.

2. Second, participants in the Ketodex group will be adaptively randomised using REDCap to three possible combinations of intranasal ketamine and intranasal dexmedetomidine in a 1:1:1 ratio for the first 150 participants: 2 mg/kg intranasal ketamine+2 μg/kg intranasal dexmedetomidine or 3 mg/kg intranasal ketamine+3 μg/kg intranasal dexmedetomidine or 4 mg/kg intranasal ketamine+2 μg/kg intranasal dexmedetomidine). After the first 150 participants, the randomisation ratio will be adapted as per above for every 50 recruited participants. The allocation ratio will be set equal to the posterior probability that a given dose is the most effective given all the available data at each interim analysis (200, 250, 300 and 350 participants). The number of participants randomised to each combination will be adapted throughout the trial to increase the number of participants receiving the more effective intranasal Ketodex combination. Intranasal Ketodex combinations will be dropped if the probability that this dose is optimal falls below 0.05. Two combinations will be dropped if there is a greater than 95% chance that a single combination is optimal. If all dose combinations have a probability of being the most effective of less than 50% after 250 participants have been enrolled in the trial, the safety profile will be evaluated to determine the most promising combination in conjunction with the data safety monitoring board (DSMB). This
will be used as the single intranasal Ketodex comparator for the remainder of the trial.

NB. Participants in the intravenous ketamine group will also undergo the second stage of randomisation but will receive saline in the identical volumes to the active drug, that is, two aliquots of 0.9% normal saline in three possible combinations: (1) 0.04 mL/kg (max 2 mL) then 0.04 mL/kg (max 4 mL), (2) 0.03 mL/kg (max 2 mL) then 0.06 mL/kg (max 6 mL) and (3) 0.02 mL/kg (max 2 mL) then 0.08 mL/kg (max 8 mL).

The allocation tables will be generated by the data coordinating centre (DCC) statistician at the Women and Children’s research Institute at the University of Alberta using R. The allocation tables across the different dose combinations will be updated at 150, 200, 250, 300 and 350 participants. An independent statistician will validate the tables and the code that was used to create them. The tables will then be provided to site pharmacies for creation of the study kits, ensuring that study staff remain blinded. Site pharmacies will prepare identically appearing study kits containing the intravenous and intranasal interventions in accordance with the allocation tables.

Blinding
Blinded parties include the participant, caregiver, research nurse videotaping the procedure and outcome assessor. Participants should not be aware of group assignment because 0.9% normal saline, dexmedetomidine and ketamine solutions are odourless, colourless and tasteless. Kits containing the interventions will be identically appearing, differing only by a study number. However, differences in onset of sedation between intravenous ketamine and intranasal Ketodex risk unblinding the sedating physician, research nurse and outcome assessor. To minimise this risk, the intravenous intervention will be given 30–40 min following the intranasal dexmedetomidine/saline sprays due to intranasal dexmedetomidine’s longer onset of action (20–30 min)24 versus intravenous ketamine (1 min).24 To increase the probability that both components of intranasal Ketodex are clinically effective at the same time, a green-labelled vial containing intranasal dexmedetomidine or saline will be administered first, followed by a white-labelled vial containing either intranasal ketamine or saline.

The research nurse will record the video of the participant’s entire body (including the face) starting immediately prior to the closed reduction and continuing until the reduction is complete. Two trained and independent outcome assessors remote from the clinical encounter and unaware of the study objectives will score sedation using the Paediatric Sedation State Scale (PSSS) (and determine the primary outcome) every 30 s for the entire length of the video. The second outcome assessor will score a randomly selected 25% sample of the participant videos to generate an inter-rater agreement. Flags will alert the outcome assessor when the closed reduction procedure is started and completed.

Unblinding procedures
The DSMB may request unblinding directly from the DCC statistician. Urgent unblinding may be done if the participant suffers an adverse event (AE), the management of which is predicated on knowing the group assignment. The research nurse will log into a secure web-based unblinding system with REDCap, where the study medication will be revealed only to the treating physician. Thus, caregivers, children and research staff, including outcome assessors, will remain blinded.

Recruitment
Potential participants will be screened and enrolled consecutively during the hours of research nurse availability (≤8 hours/day, 7 days/week). Families will provide verbal consent for eligibility screening by the research nurse. For patients who pass initial screening, the research nurse will confirm eligibility with the ED physician or their designate (any clinician who has the capacity to assess, manage and discharge a patient). If eligibility is confirmed, the research nurse will explain the study protocol and seek informed consent (and assent when appropriate) (see online supplemental files 1 and 2). Mature minor consent forms will be available for both accompanied and unaccompanied minors. Research nurse will record basic demographic features and eligibility criteria of all children with an orthopaedic injury requiring procedural sedation during their availability, whether randomised or not, to assess for enrolment bias.

Data collection
All outcomes and endpoints apart from the determination of adequate sedation (the primary outcome) will be collected by the research nurse and recorded using REDCap and a Wi-Fi-enabled iPad device.

The research nurse will record a video of the participant’s closed reduction using a Canon VIXIA HF R700 camcorder mounted on a tripod. Once data collection is completed, the video file will be uploaded onto a shared drive, which will be accessed only by the two outcome assessors. Training for the outcome assessors will consist of a 1-hour PowerPoint presentation that outlined PSSS scoring and hands-on training using videos of 25 children who underwent procedural sedation.

Following the application of a cast or splint, the research nurse will obtain satisfaction scores from the sedating provider, bedside nurse and participant. Research nurses will be trained on the recognition and definition of all expected and unexpected AEs.24–26 The research nurse will record AEs from the medical record and queries from healthcare staff during sedation and recovery. Uncertainty will be clarified with the sedating physician. All AEs will be recorded except for expected physiological effects of ketamine such as elevated blood pressure and heart rate, increased oral secretions, nystagmus, enhanced skeletal muscle tone, flushing and confusion on wakening.27 28

When the participant is awake, the research nurse will ask participants to rate their nasal irritation related to
the intranasal sprays using the FPS-R. To detect maladaptive behaviours following discharge, the caregiver will be surveyed either by telephone or automated email survey administered by REDCap 24–48 hours following discharge using the Posthospital Behaviour Questionnaire (PHBQ). A schedule of activities is shown in table 2.

**Outcome measures**

The primary efficacy outcome is adequate sedation for the duration of the procedure as we believed this to be the most salient patient-oriented outcome. Sedation will be deemed ‘adequate’ if all of the following conditions are met: (1) a PSSS score of 2 or 3 for the duration of closed reduction; (2) no additional medication is given during the procedure for the purpose of sedation; and (3) the patient did not actively resist, cry or require physical restraint for completion of the procedure. The PSSS (figure 2) is an instrument developed for assessment of sedation in children aged 1–7 years undergoing laceration repair using video scoring. The PSSS is scored from 0 to 5, with a higher number indicating a lesser degree of sedation. The PSSS assesses pain as well as oversedation and undersedation. Adequate sedation is a score of 2 or 3 and represents a level of sedation that correlates with a lack of pain, distress or oversedation or undersedation; optimal for procedural sedation as outlined by the Joint Commission, the American Academy of Paediatrics and the American Society of Anaesthesia.

Secondary outcomes include the following:

1. Length of stay is the time interval between triage and discharge.
2. Time to wakening is the time interval between the first pair or intranasal sprays to the first PSSS score of ≥3 postclosed reduction as determined by the research nurse.
3. AEs are based on Health Canada reporting standards (see online supplemental file 3). They include nasal irritation, which will be assessed using the FPS-R immediately prior to discharge and maladaptive behaviours 24–48 hours postrecovery, which will be assessed using the PHBQ. The FPS-R will be administered using an iPad, and the PHBQ will be administered through an automated email survey from REDCap or by telephone. All AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). Other endpoints are listed in table 1.

**Sample size**

Two surveys were disseminated to over 200 paediatric and general emergency physicians across Canada. We presented the case of a 5-year-old girl meeting the study’s inclusion criteria. We asked respondents to choose single-dose intravenous or intranasal ketamine for procedural sedation and to specify the largest percentage of children who failed intranasal sedation they would be willing to accept in order to routinely attempt the intranasal route first. From these surveys, the average non-inferiority margin η was 17.8%. To determine a maximum sample size, we used the Average Length Criterion (ALC) for Bayesian sample size estimation. This method selects the smallest sample size required to ensure that the 95% posterior credible interval has an average length of 0.07. We also considered four alternative randomisation strategies of intravenous ketamine to intranasal Ketodex: 1:4; 3:7; 2:3 and 1:1. The ALC determines the maximum sample size and the randomisation ratio between intravenous ketamine and intranasal Ketodex. First, we selected the smallest sample size for which the average length of the 95% posterior credible interval fell below 0.07. For this sample size, we then selected the randomisation ratio that led to the most balanced trial, provided the average length of the 95% posterior credible interval remained below 0.07. We used 2000 simulations to estimate the average posterior credible interval; the posteriors were approximated using 2000 simulation, for sample sizes increasing in increments of 10, across all four randomisation regimes. Based on this analysis, the sample size for the Ketodex trial is 410 patients randomised at a 3:2 ratio of intranasal Ketodex to intravenous ketamine.

**Statistical methods**

The results of both per protocol and intention to treat analyses will be reported for the primary outcome, with the intention-to-treat analysis being taken as the primary analysis. Demographic data will be summarised using frequencies and percentages for categorical variables and means, medians, SD and IQRs for continuous variables. Length of stay, onset of sedation and duration of sedation will be analysed using a linear dose–response model to estimate the mean duration for the optimal intranasal Ketodex combination. Adverse effects (AEs) will be analysed using a logistic dose–response model for intranasal Ketodex and a binomial distribution for intravenous ketamine. We will use logistic regression to investigate the interaction between baseline pain, measured using the FPS-R, considered as a continuous variable, and treatment effect. All inferential analyses will be undertaken using a Bayesian framework with significance declared based on posterior probabilities. We will use 95% high-density posterior credible interval estimates to report treatment effect estimates. Due to the likelihood principal, no adjustments will be made for multiplicity and type I error will be controlled through prior specification. Descriptive statistics will be reported as frequencies and percentages for discrete variables and means, medians, SD and IQRs for continuous variables. A statistical analysis plan is being published separately and includes comprehensive details of prior specification. The primary analysis will determine if the optimal intranasal Ketodex combination is non-inferior to intravenous ketamine. All other analyses will test for superiority of intranasal Ketodex. The primary analysis of the primary outcome will involve logistic regression to model the dose response relationship for the combinations of intranasal Ketodex. The optimal dose combination will
### Table 2  Schedule of activities

| Procedures                                                                 | Presenting ED visit | Prescreening | Enrolment/baseline evaluation | First pair of intranasal dexmedetomidine/saline sprays | 30–40 min after intranasal sprays | Immediately prior to closed reduction | Closed reduction | Immediately prior to cast/splint application | Immediately after cast/splint application | Immediately prior to discharge | 24–48 hours postdischarge |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs at triage*         | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Assessment of eligibility      | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Informed consent              | ×               | ×           |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Demographics                  | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Medical history                | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Randomisation (intravenous ketamine vs intranasal Ketodex)                  | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Preintervention pain score     | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Randomisation (intranasal Ketodex combinations)                             | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Administration of intranasal intervention†                                  | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Administration of intravenous intervention                                    | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Video recording begins‡         | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Video recording ongoing         | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Video recording ends            | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Satisfaction recorded from bedside nurse, sedating physician and procedure physician |                     |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Nasal irritation recorded from participant                                  | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Satisfaction recorded from participant and caregiver                         | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Adverse events recorded         | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| PHBQ§                         | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |
| Video scoring¶                 | ×               |             |                             |                                      |                                      |                                      |                             |                             |                             |                             |                             |

Continued
be the dose with the maximum posterior expected probability of adequate sedation. We will then consider whether this optimal dose is non-inferior to intravenous ketamine by computing the posterior probability of non-inferiority. If the probability of non-inferiority is above 0.97, then we will declare that intranasal Ketodex is non-inferior to intravenous ketamine. This gives a power of 0.92 to detect that the probability of adequate sedation is equal to 0.9 and a type I error rate of 4.3%. Secondary outcomes will be assessed using appropriate dose response models for intranasal Ketodex and posterior updating for intravenous ketamine. An additional analysis will investigate the interaction between baseline pain and the treatment effect.

**Interim analyses**

We will undertake seven interim analyses, at increments of 50 enrolled participants. Safety outcomes will be reviewed by the DSMB at each interim analysis. The decision to stop the trial for safety reasons will at the discretion of the DSMB. Due to the ‘unbalanced’ recruitment, the DSMB will not be blinded to treatment assignment. We will not undertake comparative effectiveness analyses at the interim analyses and will not stop for efficacy or futility.

**Missing data**

If the percentage of missing data is ≤5%, we will undertake a per protocol analysis. If the percentage of missing data is ≥5%, we will use a full Bayesian analysis to jointly model the missing data model and the outcome model. We will not undertake comparative effectiveness analyses at the interim analysis and will not stop for efficacy or futility.

**Patient and public involvement**

The study’s patient engagement partner (SH) led a group of four patient partners who informed the trial’s eligibility criteria, burden of interventions and outcomes. From their experiences as caregivers of children who visited a healthcare setting, they reviewed and provided feedback on the content of the recruitment pitch, letters of information, consent and assent. Results will not be directly disseminated to participants but will be provided on request or through access to the trial’s website (www.kidscantrials.ca/ipctnetwork).

**Data management**

Data management services will be provided by the Women and Children’s Health Research Institute (WCHRI) DCC. Study data will be entered and managed using REDCap tools hosted and supported by WCHRI. REDCap installation is electronic, web-based data capture system validated in accordance with section C.05.012 of the Health Canada Part C, Division 5 of the Food and Drug Regulations, ‘Drugs for Clinical Trials Involving Human Subjects’. Data will be entered directly into the study database using a Wi-Fi-enabled encrypted iPad. In the case of a technical failure, data will be collected on paper and then transcribed into REDCap by the research nurse or site coordinator. All data will be stored securely and in accordance with applicable regulations.

**Procedures**

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<thead>
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<th>Procedures</th>
<th>Presenting ED visit</th>
<th>Prescreening</th>
<th>First pair of intranasal dexmedetomidine/saline sprays</th>
<th>30–40 min after intranasal sprays</th>
<th>Immediately prior to closed reduction</th>
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*Vital signs are normally collected during triage and therefore will always be recorded prior to prescreening for all potential study participant.
†The maximum dose volume administered using the mucosal atomiser device is 0.5 mL per nostril. The administration of each pair of 0.5 mL sprays will be separated by at least 60 s.
‡The PHBQ will be administered either by automatic email from REDCap or by telephone, depending on the participant’s preference.
§Video recording using the Paediatric Sedation State Scale will be done by two blinded outcome assessors remote from clinical encounter.
ED, emergency department; PHBQ, posthospital behaviour questionnaire.

**Table 2** Continued
The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing REB, institutional policies or sponsor requirements. For Health Canada-regulated trials, this is 25 years. Individual participants and their research data will be identified by a unique study identification number.

**Monitoring**

Monitoring for quality and regulatory compliance will be performed by the University of Alberta’s Quality Management in Clinical Research (QMCR) office. QMCR is an independent unit housed within the university’s central administration that provides arms-length review of all University of Alberta sponsored trials, at least three times per year. Details of clinical site monitoring will be documented in a clinical monitoring plan. This trial will also be monitored federally by Health Canada (approval number HC6-24-c230863) and an institutional level by site-specific clinical research oversight bodies, as per local requirements.

Safety oversight will be under the direction of the DSMB, which will function independently of the investigators. This committee will be chaired by Dr Garth Meckler and is composed of five individuals with expertise in trial methodology, epidemiology, biostatistics and paediatric emergency medicine. The DSMB will meet at least semiannually to assess safety and efficacy data and will operate under the rules of an approved charter/terms of reference. Interim analyses will be undertaken at intervals of 50 enrolled participants. The DSMB will, in collaboration with the trial steering committee, establish safety stopping rules prior to trial initiation. The DSMB will be provided with a masked comparison between treatment groups with respect to the safety endpoints at the intervals of their choosing. At the DSMB’s request, they can receive posterior credible intervals or predictive probabilities. They can further request unmasking. The decision to stop the trial for safety reasons will be left to the discretion of the DSMB.

**LIMITATIONS**

The most important limitation of our work is our inability to procure a higher concentration of ketamine for intranasal sprays. This will result in a large number of sprays for heavier participants. Although these individuals may be more compliant with a greater number of sprays, this may impact the external generalisability of the work and translation into clinical practice. Some countries (Australia and the USA) have access to higher concentrations of intranasal ketamine (100 mg/mL) for clinical use, which may increase the clinical uptake of our findings.

**ETHICS AND DISSEMINATION**

Ethics approval was obtained from Clinical Trials Ontario (London Health Sciences Centre and McMaster Research Ethics Board #1987). The other participating sites have yet to receive ethics approval from their institutions. All protocol amendments will be submitted for approval to Health Canada before being communicated to each site. All protocol amendments will be added to the clinicaltrials.gov registration and implemented only after Health Canada and REB approval. All study participants, or their caregivers, will be notified if any new findings become available, which may be in the best medical interest of the study participant or may impact their willingness to continue participation in the study.

While long-term risks are not expected, immediate risks may occur. In terms of safety of intranasal dexmedetomidine, Kim et al. synthesised the evidence for preoperative intranasal dexmedetomidine in 11 trials of 1097 children and reported no occurrences of nausea, vomiting,
hyperglycaemia, delirium or serious adverse effects. There have been no reports of mucosal irritation, ulceration or bleeding with intranasal administration.\textsuperscript{17, 36} All AEs will be classified according to MedDRA – a multilingual standardised international medical terminology dictionary used for ‘regulatory communication and evaluation of data pertaining to medicinal products for human use.’\textsuperscript{37} Serious adverse events (SAEs) will be defined based on the Quebec guidelines\textsuperscript{20} (see online supplemental file 3). Expected and unexpected SAEs will be reported to the DSMB and Health Canada, respectively.

The study team plans to publish results in a high-impact, peer-reviewed journal and present the findings at local research days, network meetings and societal conferences. The statistical analysis plan and design paper will be published separately. Additional dissemination strategies will be developed in conjunction with our patient partners and research team. The statistical code and dataset can be made available on request.

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**Contributors** NP is the principal investigator. He developed and revised the protocol, drafted the manuscript, and will oversee study operations. KC is a research coordinator. He contributed to study design and drafting of the manuscript. He will be responsible for all study operations. DB, SS, MB, AK, OD, VS and SA are site leads at their respective institutions. They contributed to study design and drafting of the protocol and manuscript. They will be responsible for study operations at their sites. MO and PP contributed to the adaptive study methodology and drafting of the manuscript. AH and MY created the statistical analysis plan and contributed to drafting of the manuscript. TK is the nominated principal investigator for the iPCT-SPOR network. He reviewed and revised the manuscript. SH is a patient engagement partner. She led a group of other patient partners who provided input into patient-oriented outcomes, intervention administration and letters of information, consent and assent. All authors have approved the final version of the manuscript. None of the authors have financial or other conflicts of interests as they pertain to this study and its involved recruitment sites.

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**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**REFERENCES**


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Assent Letter to Participate (Ages 7 to 12)

Intranasal dexmedetomidine plus ketamine for procedural sedation in children: a randomized controlled non-inferiority multicenter trial (KetoDex Trial)

Principal Investigator: Dr. Naveen Poonai, Paediatric Emergency Physician, Children’s Hospital, London Health Sciences Centre (LHSC)

Research Ethics Board – University of Western Ontario

Why are you here?

You have a bone injury that needs to be repaired. Your doctor believes that you will need to be put to sleep so that you don’t feel pain or remember anything. Your doctor also believes that a medicine called ketamine is the best way to put you to sleep because it works very well and is very safe in kids with injuries just like yours.

Why are we doing this study?

Usually, the medicine ketamine is given through a small plastic straw in your arm. However, this is a science study and the doctors want to see if giving a different medicine by a spray in your nose is just as good as giving ketamine through the small plastic straw in your arm. The different medicine is a combination and this is called KetoDex. We need to see how sleepy the medicine makes you so we will be making a video of you during the science study. We will not share the video with anyone else but the science team. This may help us to learn a better way to help other kids with an injury like yours.

What will happen to you?

We would like to give you medicine to put you to sleep through a spray in your nose and a small plastic straw in your arm. Your mom, dad, or guardian will be asked to stay right beside you until you fall asleep. When you wake up, your bone will be fixed. After your bone is fixed, your mom, dad, or guardian will help you answer a few questions about how you felt.

Will it hurt?

When the nurses place the small plastic straw in your arm, it will hurt for a few minutes and then the pain will quickly go away. The medicine sprayed in your nose will not hurt but may feel a little funny.
**Do you have to be in this study?**

You do not have to be in this study if you don’t want to. No one will be upset with you if you do not want to do this.

**Who you should contact if you have questions?**

You can ask questions at any time now or later. If you have any questions, please talk to anyone on the research team, your family or the doctor or nurse who is taking care of you.

You can also contact:

- **Dr. Naveen Poonai** at the Children’s Hospital, London Health Sciences Centre at (519) 685-8500 x 71735 - Naveen.Poonai@lhsc.on.ca
  OR

- **Kamary Coriolano** Children’s Hospital, London Health Sciences Centre at (519) 685-8500 x 56174 - Kamary.CoriolanoDaSilva@lhsc.on.ca

- The Office of Human Research Ethics (519) 661-3036, 1-844-720-9816, email: ethics@uwo.ca.

If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Patient Relations Office at LHSC at (519) 685-8500 ext. 52036 or access the online form at: [https://apps.lhsc.on.ca/?q=forms/patient-relations-contactform](https://apps.lhsc.on.ca/?q=forms/patient-relations-contactform).
Assent Form

Research Ethics Board – University of Western Ontario

Intranasal dexmedetomidine plus ketamine for procedural sedation in children: a randomized controlled non-inferiority multicenter trial

I have read this letter and I want to participate in this study.

___________________       ________________________  ____________
Child Name (Printed)                   Child Signature                                          Date

___________________       ________________________  ____________
Person Obtaining            Signature of Person Obtaining  Date
Assent (Printed)                       Assent

Initials: _______  Version Nov 11, 2019
Informed Consent Form for Participation in a Research Study

Study Title: Intranasal dexmedetomidine plus ketamine for procedural sedation in children: an adaptive randomized controlled non-inferiority multicenter trial (KetoDex Trial)

Study Doctor: Dr. Naveen Poonai, Division of Paediatric Emergency Medicine,
Telephone: 519-685-8500 x 58134

Emergency contact number: (519) 685-8500 x 56174 – This phone number will be answered between the hours of 8:00 am to 4:00 pm only. If we are not able to take your call during this time please leave a detailed message and we will return your call as soon as possible. If this is a medical emergency, please dial 911 or go directly to your nearest emergency department.

Sponsor/Funder(s): Dr. Naveen Poonai Division of Paediatric Emergency Medicine, Canadian Institutes of Health Research, Academic Medical Association of Southwestern Ontario, Physicians’ Services Incorporated, and the Children’s Hospital Foundation, London Health Sciences Center.

Contact numbers and information are noted at the end of this document under the section heading “Contacts”.

INTRODUCTION

As a Substitute Decision Maker, you are being asked to provide informed consent on behalf of a person who is unable to provide consent for him/herself. If the participant gains the capacity to consent for him/herself, your consent for them will end. Throughout this form, “you” means the person you are representing.

You are being invited to participate in a clinical trial (a type of study that involves research). You are invited to participate in this trial because you require a medical procedure to repair a broken or dislocated bone and because you are between the ages of 4 and 17 years old. This procedure is called a closed reduction. Your doctor believes that you will need to temporarily be asleep in order to accomplish this procedure. This is called procedural sedation and we use a medication called ketamine to help you fall asleep. Ketamine is the most commonly used drug used to sedate children because it is effective at putting you to sleep, ensures that you will not be aware of the procedure or feel pain, and has an excellent safety record. However, administration of ketamine requires an intravenous line which can be distressing for children, and in some cases challenging for nurses. While this study will be exploring the use of a less distressing approach to sedation using an intranasal spray, all children participating in this study still requires an intravenous line. This is to ensure that you are safe and that you receive enough medication to put you to sleep. This study is exploring a less distressing approach to sedation using an intranasal spray. This consent form provides you with the information to make an informed decision to
participate. Please read this document carefully and feel free to ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether or not to participate in this research study.

**IS THERE A CONFLICT OF INTEREST?**
There are no conflicts of interest to declare related to this study.

If you would like additional information about the funding for this study, or about the role of the doctor in charge of this study, please speak to the study staff or the Patient Relations Office at LHSC at (519) 685-8500 ext. 52036 or access the online form at:

https://apps.lhsc.on.ca/?q=forms/patient-relations-contact-form

**WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?**

In order to safely and effectively sedate you to fix your broken or dislocated bone, we need to be able to give you medication through your vein. In order to do this, a small plastic straw is placed using a small needle which is then removed leaving the small plastic straw in your vein. This is called an intravenous line. As you may know, placing an intravenous line can be a distressing and painful experience for a child who already has an injury. However, fixing broken or dislocated bones are very common in children. In this study, we are looking for a way to diminish or eliminate the painful step of an intravenous line.

Although ketamine is usually given by an intravenous line, there is some exciting and preliminary research showing that we can use a combination of ketamine and another drug called dexmedetomidine (KetoDex) given as a spray in your nose instead of intravenous line. We call this the ‘intranasal’ route. In children, both intranasal ketamine and intranasal dexmedetomidine have been used for many procedures such as dental work, repairing cuts, MRIs, and relaxing patients before surgery. For these procedures, giving ketamine as a spray in the nose is safe, effective, and well tolerated. However, there has not been any research on giving a combination of ketamine and dexmedetomidine (KetoDex) as a spray in the nose for repairing broken or dislocated bones, which are the most common reasons children need to be put to sleep in the emergency department. Multiple sprays in the nose may be needed because we use very small amounts (0.5 mL) in each nostril. The number of nasal sprays depends on your weight. We use small amounts at a time to minimize discomfort and maximize the ability of KetoDex to put you safely to sleep. Each pair of sprays will be separated by 60 seconds. This method of delivering drugs using nasal sprays has generally been well tolerated by children.

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to show that a combination of ketamine and dexmedetomidine (KetoDex) given as a spray in the nose is just as good at putting you to sleep as giving ketamine by an intravenous line. If we can show this, it may make placing an intravenous needle unnecessary in children who require sedation. This could result in an emergency department experience that is easier, faster, and most of all less invasive, painful, and anxiety provoking for both children and their caregivers.
WHAT HAPPENS IF YOU CHOOSE NOT TO PARTICIPATE?

Participating in this study is optional. If you choose not to participate, it will not affect your care in the emergency department. You will receive ketamine using an intravenous line as this is the most commonly used approach to sedating children to repair a broken or dislocated bone.

HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?

This study will take place across six paediatric emergency departments in Canada (Children’s Hospital, London Health Sciences Centre in London, Ontario; McMaster Children’s Hospital in Hamilton, Ontario; Children’s Hospital of Eastern Ontario in Ottawa, Ontario; Stollery Children’s Hospital in Edmonton, Alberta; Winnipeg Children’s Hospital in Winnipeg, Manitoba; BC Children’s Hospital Vancouver, BC). The study will recruit 400 children and we estimate it will take two years to complete. The results should be known in about four years. We hope that the results of this study will positively impact the emergency department experience for children who require sedation to repair a broken or dislocated bone across North America.

WHAT WILL HAPPEN DURING THIS STUDY?

After looking at your x-rays, if your doctor believes that you will need to be asleep to repair your broken or dislocated bone using ketamine, he/she will ask the research nurse to determine if you are eligible for the study. If you are eligible, the research nurse will explain the study procedures in detail, answer any questions or concerns you may have, and seek informed consent (and assent when appropriate).

If you agree to participate, you will be assigned at random (like the flip of a coin) to one of two groups: intranasal ketamine and dexmedetomidine (KetoDex) as a spray in your nose or intravenous ketamine. Regardless of your group assignment, every child will need to receive both an intravenous line and nasal sprays. This is to ensure that you are safe and that you receive enough medication to put you to sleep. The number of nasal sprays depends on your weight. If you are randomly allocated to the intra-nasal group, we will be testing three different dose combinations of the ketamine and dexmedetomidine within this group. None of the three combinations is known to be any better or any worse than the others, but knowing which group is best is important for future patients.

If you are in the intranasal KetoDex group, you will receive salt water or saline through your intravenous line. If you are in the intravenous ketamine group, you will receive salt water or saline through in your nose. Neither you, the study doctor, nurse, nor research assistant can choose to which group you will be assigned.

This is a double-blind study, which means that neither you, the study doctor, nurse, nor research assistant will know which group you are in. However, your group assignment can be determined if knowing your group assignment becomes necessary for your safety. Also requests to reveal your group assignment for your information or participation in other research studies will be considered when this study is completed and the results are known.
We are primarily interested in knowing whether there is any difference between Ketodex as a spray in your nose and ketamine using an intravenous line based on the number of children that are adequately sedated. We are also interested in other important aspects of sedation such as how long it took you to fall asleep, how long you were asleep, length of stay in the emergency department, side effects, and your satisfaction with sedation.

In order to determine how well you were sedated without introducing bias, we will record a video segment of your body including your face while you are sedated. We cannot say with certainty for how long the video will be recording but we will begin just prior to receiving the study drug and ending when the closed reduction is complete. We estimate that the duration of the recording will be between 15 and 30 minutes. Your mother, father, or guardian will be encouraged to stay right by your side until you are asleep and as soon as you wake up.

For security purposes, the video will be recorded using a Canon VIXIA HF R700 camcorder (not equipped with WiFi or Bluetooth) and stored on an SD card of 32GB. The camera will be set on a 58” tripod with a 3-way pan head to provide stability. Once the video has been recorded, the research nurse will upload the video onto an online platform called Sync™. Sync™ is a Canadian cloud-based service that is in compliance with all federal and provincial data privacy guidelines. Sync’s zero-knowledge storage platform guarantees your privacy by providing end-to-end encryption and provides access only to a small group of individuals on the research team. All videos recorded and uploaded onto Sync™ will be deleted when the study is complete.

All study data obtained from you apart from the video will be uploaded and stored on a secure electronic database system known as Research Electronic Data Capture (REDCap). This will allow accurate recording of study data but more importantly, ensure that your data is not accessible to anyone outside the study group.

WHAT IS THE STUDY INTERVENTION (STUDY DRUGS)?
Ketamine, dexmedetomidine, and saline are the only medications that will be used in this study. Both ketamine and dexmedetomidine are controlled substances and their use is regulated by Health Canada. As a result, Health Canada, Clinical Trials Ontario, and the Research Ethics Boards of all participating children’s hospitals have approved all drugs used in this trial with respect to dosing and route of administration.

WHAT DATA WILL BE COLLECTED FROM YOU?
At the time of enrollment, we will need to collect some personal identifiers (name, telephone number, email address, age, sex, and hospital number). This information is needed to track side effects, describe the study sample, and allow us to communicate with you or your parent for follow up or in case you agree to participate in future studies related to ketamine. When you are ready for discharge, we will collect information on the drugs and doses used, onset and duration of sedation, length of time you
spent in the emergency department, side effects, and satisfaction from you, your caregiver, and your doctors.

Approximately 24-48 hours after discharge, the research nurse will be contacting you or your caregiver via telephone or email to screen for any late side effects based on a short survey called the Post Hospital Behavior Questionnaire. Although these are uncommon, a follow-up survey will help us identify any abnormal behaviors that may be related to sedation such as disturbances in eating, sleeping, restlessness, or anxiety.

**CAN YOU WITHDRAW FROM PARTICIPATING IN THE STUDY ONCE YOU ARE ENROLLED?**

You can choose to end your participation in this research study at any time without having to provide a reason and without affecting the quality or timeliness of your care. However, data obtained up to time you withdraw will be retained by the study team for analysis. It is important that we collect information on participants who withdraw from the study to detect any side effects. A copy of the Letters of Information, Consent, and Assent (if applicable) will be given to you for your records. The informed consent process will be conducted and documented on REDCap (including the date) before you undergo any study-related procedure or data collection.

If you decided to withdraw, please let your research nurse or anyone in the health care team know. If you decide to withdraw after you discharge, please contact Dr. Naveen Poonai at (519) 685-8500 x 58134 / naveen.poonai@lhsc.on.ca OR Kamary Coriolano at (519) 685-8500 x 56174 / kamary.coriolanodasilva@lhsc.on.ca.

**CAN YOUR DOCTOR WITHDRAW YOU FROM THE STUDY ONCE YOU ARE ENROLLED?**

Your doctor or a member of the research team may stop your participation in the study prematurely, and without your consent, for the following reasons:

- The occurrence of a side effect, laboratory abnormality, or other medical condition in which continued participation in the study would be detrimental to your health
- If you are found to meet a study exclusion criterion (either newly developed or not previously recognized)

If you are removed from this study, the study doctor or member of the research team will discuss the reasons with you and plans will be made for your continued care outside of the study. This also means that the intranasal sprays will no longer be available at this point.

**WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?**

Whether or not you choose to participate in this study, your doctor will likely sedate you for your procedure using ketamine given through an intravenous needle. Therefore, your doctor will explain the
risks that are specific to sedation to you. Long-term risks associated with ketamine and dexmedetomidine are not expected. However, intravenous ketamine is known to have short-lived side effects such as nausea, vomiting, dizziness, rash, increased eye pressure, and delirium after waking. Delirium can take the form of vivid dreams, confusion, excitement, delirium, agitation and hallucinations. Intranasal dexmedetomidine is known to have short-lived side effects such as nausea, vomiting, and lower heart rate. Serious side effects such as airway obstruction are rare in the doses and age range involved in this study. Your doctor will watch you closely to see if you have any side effects and will urgently treat them if needed.

There are no risks that are specific to ketamine or dexmedetomidine given as a spray in your nose beyond those associated with ketamine or dexmedetomidine alone. However, it may take you a little bit longer to fall asleep and the duration of your sleep may be slightly longer. If your doctor believes you are not asleep, additional intravenous ketamine will be given to make sure that you are not in pain and not aware of the procedure being performed.

If you experience side effects that you believe require a hospital visit, it is important that you make every effort to return to the hospital where sedation was performed. If you need immediate treatment and are unable to return to the hospital, the study doctor should be contacted as soon as possible.

WHAT ARE THE REPRODUCTIVE RISKS?

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, patients who report that they may be pregnant will be excluded.

Given the duration of the study, single treatment, and the anticipated age group of the target population under study, it is not anticipated that pregnancy will be an issue. However, should the participating Site Investigator become aware that the participant was unknowingly pregnant during participation in the study he/she will report the pregnancy in accordance with their responsible Research Ethics Board guidelines and to the Qualified Principal Investigator within 24 hours of becoming aware of the event.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Benefits

There will be no direct benefit to you for participating in the study, but it may help to improve the care of children in the future who require sedation to repair a broken or dislocated bone.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the research team will only collect the information they need for this study. All information collected will be kept confidential and will not be part of your medical
record. You will be assigned a unique identification number that contains no personal identifiers. This number will appear on all the information we collect from the study. Research data will be stored electronically in REDCap at the Women and Children’s Health Research Institute (WCHRI) and Data Coordinating Centre (DCC) at the University of Alberta. The personnel at this center have the expertise to maintain quality standards to ensure your privacy. Paper forms (Letters of Information, Consent, and Assent if applicable) will be stored for 25 years according to Health Canada’s policies in a locked and secure research cupboard that is accessible only to the research team. Video segments will only be accessible to a limited number of people on the research team and will be deleted at the end of the study.

Who will conduct the onsite monitoring of the study at the centres?

University of Alberta is the sponsor organization and, the Quality Managements in Clinical Research Office (QMCR) at the University of Alberta will be providing onsite monitoring of the study at the participating Canadian centres.

Study monitoring is the action of supervising the progress of a clinical study to ensure that the study is being conducted, recorded, and reported in accordance with the protocol and all norms and regulations according the Health Canada.

Will the study data be entered into a database for future use?

Following your participation, your identity will not be revealed. Any report published as a result of this study will not identify you by name. By signing the consent form, you give permission to the research team to access only personal health information that we deem necessary for conduct of the research study.

You are also giving permission to the following organizations to have access to study related information (including personal health information) to ensure that the study is following the proper laws and regulations:

- Dr. Naveen Poonai
- Representatives of Western University’s Health Sciences Research Ethics Board,
- Health Canada (because Health Canada oversee the use of natural health products/drugs/devices in Canada) to have access to study related information (including personal health information) to ensure that the study is following the proper laws and regulations.

Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that is sent to the research ethics board for this study. Your name, address, or other information that may directly identify you will not be used. The records received by these organizations may contain your participant code, initials, sex, and date of birth, type of intervention given during your visit to emergency department.
A copy of the consent form that you sign to enter the study may be included in your health record/hospital chart.

**MANDATORY SAMPLE COLLECTION**

We are not collecting any samples in this study.

**WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?**

- Tell the research nurse about your current medical conditions, including all prescription and non-prescription medications and supplements. This is for your safety as these may interact with the study drugs.
- Tell the study doctor if you are thinking about participating in another research study.
- Tell the study doctor if you become pregnant or father a child while participating on this study.

**HOW LONG WILL YOU BE IN THIS STUDY?**

Participation in the study while you are in the emergency department will last for about one to two hours from the time you sign the Letters of Information, Consent, and Assent (if applicable) to the time you wake up from sedation. You will be discharged home as soon as you are awake and your physician believes that you are safe to be sent home. The time to wake up from sedation may vary between individuals. The research nurse will contact you either by phone or email 24-48 hours after discharge to complete the follow-up survey. The survey should take approximately 10-15 minutes to complete and can be done over the phone or online.

**WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN THIS STUDY?**

Your family doctor/health care provider will be informed by the research team that your child is taking part in the study, if you wish. You will be provided with a letter explaining that your child is taking part in the study and you may give it to your doctor/health care provider in the event that you require further care.

**WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?**

The trial’s objectives, protocol, and potential implications will be featured on the study’s website (www.ketodexmed.ca) with navigation tabs for specific stakeholders: investigators, caregivers, children, and clinicians. A detailed description of the study’s protocol will be listed on www.clinicaltrials.gov, an international clinical trial registry. The study’s protocol and findings will be submitted for publication to a medical journal and may be presented at international conferences and local research meetings. This study will comply with the Canadian Institute of Health Research Open Access Policy which means that the research findings will be freely accessible to everyone. However, any information that can identify
you such as name, address, date of birth, etc. will not appear on any website, publication, or presentation. For the reasons of transparency and education, it is strongly encouraged by many medical journals and other authorities to publish the anonymized data from clinical studies for public use. Examples of anonymized data from this study include type of fracture or dislocation, level of pain characterized by a number, level of satisfaction with the sedation also characterized by a number, etc. While anonymized data may be retained indefinitely, as per institutional policies, only identifiable information must be deleted after the data retention period (25 years for Health Canada studies). The anonymized data is visible to researchers or the general public after the study is over. Future researchers may use anonymized data to improve knowledge about procedural sedation in children (7 – 17 years) presenting to paediatric emergency departments with a fracture or dislocation.

WHAT IS THE COST TO PARTICIPANTS?

There are no costs to participation in this study.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

If you decide to participate in this study, you will be offered a token of appreciation in the amount of $50 that will be mailed to your home after discharge from the emergency department.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You have the right to be informed of the results of this study once the entire study is complete. A summary of the results will be publicly available at http://www.clinicaltrials.gov.

Your rights to privacy are legally protected by Canadian federal and provincial laws that require safeguards to ensure that your privacy is respected.

The rights and welfare of your participation will be protected by emphasizing to you that the quality of your medical care will not be adversely affected if you decline to participate in this study. Furthermore, by signing this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have any questions or concerns, feel free to contact:

- Dr. Naveen Poonai at the Children’s Hospital, London Health Sciences Centre at (519) 685-8500 x 71735 - Naveen.Poonai@lhsc.on.ca

OR

London Health Science Centre 800 Commissioners Road East, Room E4-221, London, Ontario, N6A 5W9


- **Kamary Coriolano** Children’s Hospital, London Health Sciences Centre at (519) 685-8500 x 56174 - Kamary.CoriolanoDaSilva@lhsc.on.ca

- The Office of Human Research Ethics (519) 661-3036, 1-844-720-9816, email: ethics@uwo.ca.

If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Patient Relations Office at LHSC at (519) 685-8500 ext. 52036 or access the online form at: [https://apps.lhsc.on.ca/?q=forms/patient-relations-contactform](https://apps.lhsc.on.ca/?q=forms/patient-relations-contactform).

You will receive a copy of this information form after enrolling in the study.
Study title: Intranasal dexmedetomidine plus ketamine for procedural sedation in children: an adaptive randomized controlled non-inferiority multicenter trial (KetoDex Trial)

SIGNATURES

- All of my questions have been answered.
- I understand the information within this informed consent form.
- I allow access to my medical records as explained in this consent form,
- I do not give up any of my legal rights by signing this consent form.
- I agree or agree to allow the person I am responsible for, to take part in this study.
- I understand that if I do not agree, I do not need to participate.

May we contact you for future studies related to ketamine and to this study?

Indicate: ☐ Yes ☐ No

__________________________  ____________________________  ________________
Signature of Participant     PRINTED NAME               Date

__________________________  ____________________________  ________________
Substitute Decision Maker   PRINTED NAME               Date

__________________________  ____________________________  ________________
Signature of Person Conducting Consent Discussion  PRINTED NAME & ROLE  Date

Complete the following section only if the participant is unable to read or requires an oral translation:

If the participant is assisted during the consent process, please check the relevant box

London Health Science Centre 800 Commissioners Road East, Room E4-221, London, Ontario, N6A 5W9

Version date of this form: 08 of September, 2020 V.1.5

Initials
and complete the signature space below:

☐ The person signing below acted as an interpreter, and attests that the study as set out in the consent form was accurately sight translated and/or interpreted, and that interpretation was provided on questions, responses and additional discussion arising from this process.

Note: Family members are not allowed to act as a partial witness

Note: Healthcare providers are not allowed to act as a partial witness

____________________________ ______________________  _________________
Signature of Impartial  PRINTED NAME Date
Translator
(If participant were unable to read/required an oral translation)

Language: ________________________________

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to the participant, and any questions have been answered.

____________________________ ______________________  _________________
PRINT NAME  Signature  Date
of witness

____________________________
Relationship to Participant

Please note: More information regarding the assistance provided during the consent process should be noted in the medical record for the participant if applicable, noting the role or relationship of the impartial witness.
Adverse events (AEs) document medical events that occur to a participant/subject once enrolled in a study. AEs are the construct through which the safety of an intervention is recorded and assessed during a study.

Recording Adverse Events: All AEs, both serious and non-serious, regardless of relationship to the study intervention, should be recorded on the AE case report form (CRF). AE data should be collected from the time the informed consent form is signed through the duration of the study.

Please use standard medical terminology when recording AEs.

Definitions and Instructions:
Adverse Event: Any adverse occurrence in the health of a clinical trial subject who is administered a drug that may or may not be caused by the administration of the drug, and includes an adverse drug reaction. Each AE should be listed on a separate line in the table below. Worsening of a baseline condition should be listed as an AE. Events such as headache and sinus pain should be listed as separate events.

Serious Adverse Event: An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the Site Investigator or Sponsor/Principal investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Start Date: Record the date the adverse event started. The date should be recorded to the level of granularity known and in the specified format. If a previously recorded AE worsens, a new record should be created with a new start date. There should be no AE start date prior to the date of informed consent. If an item recorded on the medical history worsens during the study, the date the AE worsened is entered as the start date.

End Date: Record the date the adverse event stopped/resolved or worsened. The date should be recorded to the level of granularity known and in the specified format. If an AE worsens, record an end date and create a new AE record with a new start date and severity.

Severity: Severity is not synonymous with seriousness. A severe rash is not likely to be an SAE. Likewise, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day’s hospitalization and thus is an SAE. Adverse Events will be assessed for severity by the site qualified investigator using the following definitions of severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Note: The term “severe” does not necessarily equate to “serious”.

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Relatedness: All adverse events (AEs) must have their relationship to study intervention assessed by the site qualified investigator/clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. Definitions can be found below:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with the use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

**Action Taken with Study Intervention:** Was it required to stop the study intervention? Choose treatment course in the table below.

**Expectedness:** The site qualified investigator or co-investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. Choose either Yes or No in the table below.

**Outcome:** The outcome of an AE may not be captured at the visit during which it was first reported, but must be captured to provide a complete picture of the event. Entering the outcome of an AE may be deferred until the AE is resolved, or the participant/subject completes the study. For AEs that have not resolved at the time of a study visit, the outcome should be marked as “unresolved” on the AE case report form.

**Serious?** Choose either Yes or No. This question should only be answered YES if the outcome of the AE meets the definition of SAE listed above. Further information will be required if the AE is classified as Serious. See “Serious Adverse Events” in the study protocol.
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| Site ID: | Participant Study ID: LHSC__|__|__ |

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**Adverse Event Description** – For each item below please provide the following information. Please be as concise as possible. Enter a diagnosis, where available. If a formal diagnosis is not known enter a concise description of the event, including signs and symptoms. Research nurse should complete the form and the site PI will review and sign.

<table>
<thead>
<tr>
<th>Adverse Event Description</th>
<th>Start Date [YYYY/MM/DD]</th>
<th>Severity</th>
<th>Relationship to Study Intervention</th>
<th>Action Taken</th>
<th>Expected</th>
<th>Outcome</th>
<th>Serious?</th>
<th>End Date DD/MM/YYYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>□ Retching/Vomiting</td>
<td></td>
<td>□ Mild</td>
<td>□ Not Related</td>
<td>□ None</td>
<td>□ Yes</td>
<td>Recovered/Resolved</td>
<td>□ Yes*</td>
<td>No</td>
</tr>
<tr>
<td>□ Nausea</td>
<td></td>
<td>□ Moderate</td>
<td>□ Unlikely to be related</td>
<td>□ Study Intervention Interrupted</td>
<td>□ No</td>
<td>Recovered/Resolved with Sequela</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>□ Abdominal pain</td>
<td></td>
<td>□ Severe</td>
<td>□ Potentially Related</td>
<td>□ Study Intervention Discontinued</td>
<td></td>
<td>Recovering / Resolving</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>□ Seizure</td>
<td></td>
<td>□ Life-threatening or Disabling</td>
<td>□ Probably Related</td>
<td>□ Study Intervention Modified</td>
<td></td>
<td>Unresolved / Not Recovered</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>□ Hypersensitivity</td>
<td></td>
<td>□ Fatal/Death</td>
<td>□ Definitely Related</td>
<td>□ Other (specify)</td>
<td></td>
<td>Fatal</td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>□ Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>□ Emergency Reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>□ Other:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

| 2. Integumentary         |                         |          |                                    |               |         |         | Yes*    | Yes*               |
| □ Rash                   |                         | □ Mild   | □ Not Related                      | □ None        | □ Yes   | Recovered/Resolved | □ Yes*       | No                  |
| □ Itching                |                         | □ Moderate| □ Unlikely to be related           | □ Study Intervention Interrupted | □ No    | Recovered/Resolved with Sequela | No          |  No                 |
| □ Rash                   |                         | □ Severe | □ Potentially Related              | □ Study Intervention Discontinued |         | Recovering / Resolving   | No          |  No                 |
| □ Life-threatening or    |                         | □ Probably Related | □ Study Intervention Modified |         |         |         |         | Yes*               |
|   Disabling              |                         | □ Definitely Related | □ Other (specify) |         |         |         | Yes*    | Yes*               |
| □ Fatal/Death            |                         |           |                                    |               |         |         | Yes*    | Yes*               |

*Yes, should be answered when the adverse event results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

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<table>
<thead>
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<th>Action Taken</th>
<th>Expected</th>
<th>Outcome</th>
<th>Serious?</th>
<th>End Date DD/MM/YYYY</th>
</tr>
</thead>
</table>
| 3. Cardiovascular – Bradycardia (2 SDs below normal for age)  
Bradycardia AND at least one of the following interventions:  
- Vigorous tactile stimulation  
- Airway repositioning  
- Suctioning  
- Supplemental or increased oxygen  
- Oral or nasal airway  
- Positive pressure ventilation  
- Endotracheal intubation  
- Chest compressions  
- Administration of medications: | | | | | | | | |
| | □ Mild  
□ Moderate  
□ Severe  
□ Life-threatening or Disabling  
□ Fatal/Death | □ Not Related  
□ Unlikely to be related  
□ Potentially Related  
□ Probably Related  
□ Definitely Related | □ None  
□ Study Intervention Interrupted  
□ Study Intervention Discontinued  
□ Study Intervention Modified  
□ Other (specify) | □ Yes  
□ No | □ Recovered/Resolved  
□ Recovered/Resolved with Sequelae  
□ Recovering / Resolving  
□ Unresolved / Not Recovered  
□ Fatal  
□ Unknown | □ Yes*  
□ No |
| 4. Cardiovascular – Hypotension (SBP < 5th %ile for age)  
Hypotension AND at least one of the following interventions:  
- IV fluid  
- Chest compressions  
- Administration of medications: | | | | | | | | |
| | □ Mild  
□ Moderate  
□ Severe  
□ Life-threatening or Disabling  
□ Fatal/Death | □ Not Related  
□ Unlikely to be related  
□ Potentially Related  
□ Probably Related  
□ Definitely Related | □ None  
□ Study Intervention Interrupted  
□ Study Intervention Discontinued  
□ Study Intervention Modified  
□ Other (specify) | □ Yes  
□ No | □ Recovered/Resolved  
□ Recovered/Resolved with Sequelae  
□ Recovering / Resolving  
□ Unresolved / Not Recovered  
□ Fatal  
□ Unknown | □ Yes*  
□ No |

* Yes, should be answered when the adverse event results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

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<tbody>
<tr>
<td>5. Oxygenation</td>
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<td>Desaturation (SpO2 &lt; 90%) AND at least one of the following:</td>
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<td></td>
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<tr>
<td>□ Vigorous tactile stimulation</td>
<td>□ Unlikely to be related</td>
<td>□ None</td>
<td>□ Yes*</td>
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<tr>
<td>□ Airway repositioning</td>
<td>□ Potentially Related</td>
<td>□ Yes</td>
<td>□ No</td>
<td></td>
<td></td>
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<tr>
<td>□ Suctioning</td>
<td>□ Definitely Related</td>
<td></td>
<td>□ Yes*</td>
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<tr>
<td>□ Supplemental or increased oxygen</td>
<td>□ Other (specify)</td>
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<tr>
<td>□ Oral or nasal airway</td>
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<tr>
<td>□ Positive pressure ventilation</td>
<td></td>
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<tr>
<td>□ Endotracheal intubation</td>
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</table>

| 6. Central Apnea |                         |          |                                   |              |         |         |         |
| Cessation or pause in ventilator effort AND at least one of the following interventions: |                         |          |                                   |              |         |         |         |
| □ Vigorous tactile stimulation  | □ Unlikely to be related  | □ None   | □ Yes*                            |         |         |         |         |
| □ Airway repositioning    | □ Potentially Related  | □ Yes    | □ No                              |         |         |         |         |
| □ Suctioning              | □ Definitely Related    |          | □ Yes*                            |         |         |         |         |
| □ Supplemental or increased oxygen | □ Other (specify)       |          |                                   |         |         |         |         |
| □ Oral or nasal airway    |                         |          |                                   |         |         |         |         |
| □ Positive pressure ventilation |                   |          |                                   |         |         |         |         |
| □ Endotracheal intubation |                         |          |                                   |         |         |         |         |
| □ Administration of reversal agent (nalozone, flumazenil, etc.): |                         |          |                                   |         |         |         |         |

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<tbody>
<tr>
<td>7. Obstructive Apnea – Partial Upper Airway Obstruction</td>
<td></td>
<td></td>
<td>Not Related</td>
<td>None</td>
<td>Yes</td>
<td>Recovered/Resolved with Sequelae</td>
<td>Yes*</td>
<td>No</td>
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<tr>
<td></td>
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<td>Unlikely to be related</td>
<td>Study Intervention Interrupted</td>
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<td>Probably Related</td>
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<td></td>
<td>Definitely Related</td>
<td>Study Intervention Modified</td>
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<td>Other (specify)</td>
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<tr>
<td>8. Obstructive Apnea - Complete Upper Airway Obstruction</td>
<td></td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Yes</td>
<td>Recovered/Resolved with Sequelae</td>
<td>Yes*</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>Unlikely to be related</td>
<td>Study Intervention Interrupted</td>
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<td>Potentially Related</td>
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<td>Fatal/Death</td>
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<tbody>
<tr>
<td>9. Laryngospasm</td>
<td></td>
<td>□ Mild □ Moderate □ Severe □ Life-threatening or Disabling □ Fatal/Death</td>
<td>□ Not Related □ Unlikely to be related □ Potentially Related □ Probably Related □ Definitely Related</td>
<td>□ None □ Study Intervention Interrupted □ Study Intervention Discontinued □ Study Intervention Modified □ Other (specify)</td>
<td>□ Yes □ No</td>
<td>□ Recovered/Resolved □ Recovered/Resolved with Sequelae □ Recovering / Resolving □ Unresolved / Not Recovered □ Fatal □ Unknown</td>
<td>□ Yes* □ No</td>
<td></td>
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</table>

10. Pulmonary Aspiration
Suspicion or confirmation of oropharyngeal or gastric contents in the trachea during the sedation or physiologic recovery phase and the appearance of respiratory signs and symptoms that appear before the participant is awake and were not present before the sedation. These include:
□ Cough □ Crackles □ Decreased breath sounds □ Tachypnea □ Wheeze □ Rhonchi □ Respiratory distress □ Supplemental oxygen for decreased saturation □ CXR with focal infiltrate, consolidation, or atelectasis

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<tbody>
<tr>
<td>11. Neurologic</td>
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<td>□ Mild</td>
<td>□ Not Related</td>
<td>□ None</td>
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<td>□ Recovered/Resolved</td>
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<td>□ Yes/MM/YYYY</td>
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<tr>
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<td></td>
<td>□ Moderate</td>
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<td>□ Unknown</td>
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<tr>
<td>12. Behavioral</td>
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<td>□ Mild</td>
<td>□ Not Related</td>
<td>□ None</td>
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<td></td>
<td>□ Seizure</td>
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<tbody>
<tr>
<td>13. Unpleasant recovery reactions</td>
<td>☐</td>
<td>Mild</td>
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<td>☐ No</td>
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<td>Moderate</td>
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<td>☐ Recovered/Resolved with Sequelae</td>
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<td>14. Permanent Complications</td>
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<td>15. Other</td>
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<tr>
<td>□ Any other event that meets the adverse event definition in the protocol but which is not included above.</td>
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<td>□ Fatal/Death</td>
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Investigator Signature

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